The Examiner has indicated that the specification should be amended to indicate Applicant's claim for priority in the present application. Applicants have submitted herewith a substitute specification which has been amended to include a priority claim on the first page of the specification.

Typographical Errors/Trademarks

The Examiner has requested that Applicants review the specification and correct spelling and typographical errors, as well as insert proper trademark indication. Applicants have submitted herewith a substitute specification which has been amended to correct typographical errors, and insert proper trademark where required.

Applicants submit that the substitute specification filed herewith has been amended only to remedy formal deficiencies indicated by the Examiner, and does not include any new matter.

Rejection of Claims 1-14, 17-18, 21-25, 28-29, and 69-70 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-14, 17-18, 21-25, 28-29, and 69-70 under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the invention. In particular, the Examiner, after imposing an election of a species of CD40 ligand for prosecution, has now asserted that the metes and bounds of a "CD40 ligand enhanced cell" and an "engineered ligand for CD40" are ambiguous in light of the elected species. Applicants submit that the claims are definite as written.

The claims of the present invention relate to a "CD40 ligand-enhanced cell" comprising an "exogenous engineered ligand for CD40". The specification defines a "CD40 ligand-enhanced cell" as a cell which has been mixed with an exogenous ligand for CD40, and has antigen either contained in or attached to the cell (page 3, line 3-4). The specification defines an exogenous ligand for CD40 as a ligand for CD40 which is introduced from or produced outside the cell (page 9, lines 25-26). The specification teaches further that a CD40 ligand may be CD154, or an antibody to CD40 (page 15-16). The specification defines an "engineered ligand for CD40" as a ligand for CD40 that comprises a heterologous cell membrane binding moiety (page 10, lines 31-32). The specification defines a "cell membrane binding moiety" as a moiety

through which a molecule can be stably bound to a cell and includes crosslinking moieties, and lipid moieties (page 12, lines 19-21). Thus, the specification clearly defines the metes and bounds of a CD40 ligand-enhanced cell" and an "engineered ligand for CD40".

The Examiner asserts that the claims are indefinite because it is not clear whether a CD40 ligand is incorporated into or onto the cell or provided as a separate element of the composition. Applicants submit that the claims clearly recite a "CD40 ligand enhanced cell" which is defined in the specification as a cell which has been mixed with an exogenous ligand for CD40, and further where the CD40 ligand is engineered (i.e., comprises a heterologous cell membrane binding domain). Thus, in keeping with the notice function served by §112, second paragraph, one of skill in the art, upon reading the language of the present claims would be apprised of the fact that the claim covers a method of vaccinating a mammal by administering a composition comprising an antigen bearing cell (i.e., a cell which either expresses an antigen or has antigen associated with its membrane) and an engineered CD40 ligand. The fact that the engineered CD40 ligand is advantageously designed to permit association with the cell membrane, does not make the claim unclear. One of skill in the art would know from the claim language that administering a composition comprising an antigen bearing cell and an engineered CD40 ligand (i.e., CD40 ligand comprising a heterologous cell membrane binding moiety) would fall under the claim. The Examiner has not indicated why one of skill in the art would reach a contrary conclusion.

With respect to the Examiner's assertion that the metes and bounds of an engineered ligand for CD40 "particularly as it reads on [a] CD40-specific antibody" are ambiguous. Applicants submit, as noted above, that the claims, when read in view of the specification, are clear. One of skill in the art, given the teaching in the specification that a CD40 ligand may be an antibody to CD40, would clearly be appraised that if he/she where to practice a method of vaccination of a mammal using a composition comprising an antigen bearing cell mixed with an engineered antibody for CD40, (i.e., a CD40 ligand; whether a polyclonal, monoclonal, humanized, etc.), then they would fall under the instant claims. Applicants respectfully submit that to require more extensive limitation of the claims in the name of meeting the requirements of §112, second paragraph, raises the standard for definiteness above that required by the MPEP, and supported by relevant case law.

Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1, 2, 5-9 and 15 Under 35 U.S.C. §102(e)

The Examiner has rejected claims 1, 2, 5-9 and 15 under 35 U.S.C. §102(e) as being anticipated by Maraskovsky et al. (U.S. Pat. no. 6,017,527). The Examiner asserts that Maraskovsky teach methods of vaccination with antigen-expressing activated dendritic cells, including stimulating immune responses with the administration of other cytokines such as the CD40 ligand. Applicants submit that the present claims are not anticipated by the teachings of Maraskovsky.

The present claims relate to methods for vaccinating a mammal to a selected antigen comprising administering to the mammal a vaccine comprising a CD40 ligand-enhanced cell, wherein the CD40 ligand of the CD40 ligand-enhanced cell is engineered (that is, comprises a heterologous cell membrane binding moiety). The present specification defines an engineered CD40 ligand as a ligand for CD40 that comprises a heterologous cell membrane binding moiety (page 10, lines 30-32). The Examiner asserts that the CD40 ligand taught by Maraskovsky would be engineered or recombinantly made. Applicants submit that there is no teaching in Maraskovsky which provides that the CD40 ligand comprises a heterologous cell membrane binding moiety, and is thus engineered. Applicants respectfully remind the Examiner that "engineered" in the context of the present invention does not merely mean that the CD40 ligand is produced recombinantly, but instead requires that the CD40 ligand include a heterologous cell membrane binding moiety.

Accordingly, Applicants submit that Maraskovsky do not teach CD40 ligand enhanced cells comprising an engineered CD40 ligand, and further does not teach a CD40 ligand enhanced cell which includes antigen contained in or attached to the cell. Applicants therefore request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1, 2, 5-9, and 15 Under 35 U.S.C. 103(a)

The Examiner has rejected claims 1, 2, 5-9, and 15 under 35 U.S.C. §103(a) as being unpatentable over Maraskovsky et al. in view of Dullforce et al. (Nature Medicine, 4: 88, 1998),

and/or Heath et al. (Eur. J. Immunol., 24: 1828, 1994), and/or Caux et al. (Research in Immunology 145: 235, 1994). The Examiner asserts that Maraskovsky teach the methods of vaccination with antigen-expressing activated dendritic cells, including stimulating immune responses with the administration of other cytokines such as the CD40 ligand. The Examiner notes that Maraskovsky does not teach the administration of agonistic CD40-specific antibodies per se. The Examiner asserts that each of Dullforce, Heath, and Caux teach anti CD40 antibodies which are capable of stimulating immune responses. The Examiner implies that it would have been obvious to one of skill in the art to combine the teachings of anti-CD40 antibodies as taught by Dullforce, Heath, and/or Caux with the "antigen" expressing activated dendritic cells as taught by Maraskovsky to arrive at the present invention. Applicants respectfully disagree.

For the reasons described below, the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. *Id.* The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest *all the claim limitations*. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

The cited combination does not teach all the claim limitations

Applicants submit that combined teachings of the references cited by the Examiner do not result in the claimed invention. As discussed above, Maraskovsky teaches that activated dendritic cells which present processed antigen on their surface and which may be mixed with CD40 ligand, elicit an immune response. As discussed above, Maraskovsky does not teach an engineered CD40 ligand which comprises a heterologous cell membrane binding moiety. The deficiencies in the teachings of Maraskovsky are not remedied by the teachings provided by

Dullforce, Heath, or Caux. None of Dullforce, Heath, or Caux teach an engineered CD40 ligand, or any other engineered proteins. Thus, the combination of the teachings of Dullforce, Heath, or Caux with Maraskovsky do not result in a vaccine composition comprising a CD40 ligand enhanced cell comprising an engineered CD40 ligand and an antigen.

Accordingly, Applicants submit that the invention is non-obvious over the teachings of Maraskovsky in combination with one or more of Dullforce, Heath, or Caux. Applicants therefore request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1, 2, 5-14, 17-18, 21-25, 28, 29, and 69 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 2, 5-14, 17-18, 21-25, 28, 29, and 69 under 35 U.S.C. §103(a) as being obvious over Maraskovsky, in view of Dullforce, Heath, and Caux, and in further view of McHugh et al. (PNAS, 92: 8059, 1995). Applicants respectfully disagree.

Applicants have discussed previously the reasons why the present invention is not obvious over the teachings of Maraskovsky in view of Dullforce, Heath, and Caux. The Examiner is now adding the teachings of McHugh and the teachings of the present specification with respect to membrane attachment moieties to suggest that the claimed invention is obvious. Applicants submit that there is no motivation to make the combination suggested by the Examiner.

Maraskovsky teaches two primary embodiments for combining dendritic cells with a CD40 binding protein. In the first, the specification teaches that the dendritic cells, which express CD40 on their surface, are mixed with a CD40 binding protein in order to activate the dendritic cells to process antigen (col. 2, lines 1-2; 8-9). In the second embodiment, the specification teaches that the activated dendritic cells can be "administered to the individual prior to, concurrently with or subsequent to administration of cytokines that modulate an immune response, for example a CD40 binding protein (**i.e., soluble CD40L**)" (col. 2, lines 15-19; emphasis added). The specification further teaches that a particularly preferred cytokine is CD40 ligand, and that a "soluble form" has been described (col. 11, lines 59-60). Moreover, the other cytokines and immunostimulatory molecules taught by Maraskovsky which can be administered along with an activated dendritic cell are soluble (see, e.g., col. 11, lines 50-60). Thus,

Maraskovsky clearly teaches the co-administration of a soluble cytokine and an activated dendritic cell.

Applicants submit the McHugh teaches a construct comprising a GPI moiety fused to B7 molecules (also referred to as CD80), and the use of the fusion protein, incorporated into the membrane of tumor cells, to provide a costimulatory signal needed to stimulate T cells. Applicants submit that not only does McHugh not teach or even suggest the use of a GPI moiety linked to CD40 ligand (i.e., an engineered CD40 ligand), or the use of such an engineered CD40 ligand in a mixture with an antigen bearing cell for the purpose of vaccinating a mammal, but McHugh also acknowledges that the specific teachings relating to GPI-B7 are unpredictable. McHugh teaches at page 8063, first full paragraph, that the stability of GPI-B7 on the surface of irradiated tumor cells is limited. Moreover, McHugh teaches that the "*in vivo* kinetics for the induction of an anti-tumor immune response has yet to be elucidated and may differ between systems". Nevertheless, the Examiner asserts that one of skill in the art would have been motivated to create membrane linked anti-CD40 antibodies to mix with the activated dendritic cells of Maraskovsky, despite Maraskovsky's teaching that the cytokine should be soluble, and in view of the acknowledgment in McHugh that the GPI linked system may differ from system to system.

Applicants submit that neither the references, nor the knowledge of those skilled in the art would provide the motivation to make the combination suggested by the Examiner. Maraskovsky, in fact, teaches away from using an engineered CD40 ligand (i.e., comprising a heterologous cell membrane binding moiety), because Maraskovsky teaches that the activated dendritic cells are to be mixed with <u>soluble</u> immunostimulatory factors. In addition there is likewise no teaching in McHugh that would motivate the combination, particularly in view of the fact that McHugh teaches that the use of a GPI-linked protein to stimulate an immune response may differ from system to system (e.g., between a GPI-linked B7 molecule and a GPI-linked CD40 ligand). The Examiner asserts that McHugh teaches combinations of costimulatory signals to create the optimal target to facilitate T cell regulatory and effector functions. Applicants submit, McHugh contains no teaching or suggestion that the GPI moiety may or should be combined with a ligand for CD40 to stimulate an immune response. Applicants

submit further that none of Dullforce, Heath, and Caux provide the motivation necessary to make the combination suggested by the Examiner.

In addition, McHugh teaches that the GPI moiety is to be coupled to the C-terminal end of a desired protein. Applicants submit, however that, as shown in Exhibit A (GenBank Accession No P29965), the C-terminus of the CD40 ligand is extracelluar. That is, it is the C-terminus of the CD40 ligand which is likely to bind to CD40. Since, as taught by McHugh, GPI moieties link to the carboxy-terminus of proteins, one of skill in the art would expect that the attachment of a GPI moiety to the C-terminus of CD40 ligand would interfere with the binding of CD40 ligand to its receptor. Thus, one of skill in the art would not have been motivated, absent the teachings of the present invention, to modify a CD40 ligand by attaching a carboxy-terminal GPI moiety. Where the CD40 ligand is an antibody to CD40, Applicants submit that one of skill in the art would be likewise unmotivated to combine the teachings of Maraskovsky, Dullforce, Heath, and Caux, cumulatively relating to soluble CD40 binding proteins, with the GPI moieties taught by McHugh, because one of skill in the art would not be able to predict how the attachment of a GPI moiety to the C-terminus of a soluble anti-CD40 antibody would affect the ability of the antibody to bind CD40. In fact, as noted above, McHugh teaches that the immune response elicited by different molecules coupled to GPI may differ.

Accordingly, applicants submit that the invention is not obvious over the teachings of Maraskovsky alone or in combination with Dullforce, Heath, Caux, and/or McHugh. Applicants therefore request that the rejection be reconsidered and withdrawn.

Rejection of Claims 3, 4, and 70 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 3, 4, and 70 under 35 U.S.C. § 103(a) as being obvious over the combination of Maraskovsky, Dullforce/Heath/Caux, and McHugh and further in view of Jacquier-Sarlin et al. (Immunology 84: 164, 1995).

The Examiner asserts that the previous combination differed from the claimed invention in that the prior combination did not teach the addition of the alpha chain of C3b. The Examiner asserts that Jacquier-Sarlin teaches the alpha chain of C3b. Applicants submit that, as described above, there is no motivation to combine the teachings of Maraskovsky, Dullforce, Heath, Caux,

and/or McHugh, and further, that even if the references were combined (with respect to Maraskovsky, Dullforce, Heath, and Caux) the resulting combination would not teach the claimed invention. Applicants submit that the teachings of Jacquier-Sarlin do not remedy the deficiencies in the teachings of the other references, and therefore cannot be combined with the previously cited references to render the invention obvious. Jacquier-Sarlin merely teaches the ability of the complement fragment C3b to modulate antigen processing. Jacquier-Sarlin does not teach CD40 ligand, or a method of vaccinating an animal comprising administering a CD40 ligand enhanced cell which comprises an engineered ligand for CD40. Jacquier-Sarlin does not teach an engineered CD40 ligand, and does not provide teachings which would remedy the fact that Maraskovsky teaches away from combining the teachings therein relating to soluble immunostimulatory molecules with the teachings of membrane bound immunostimulatory molecules taught by McHugh.

Accordingly Applicants submit that the claims are non-obvious in view of Jacquier-Sarlin taken alone, or in combination with the other cited references. Applicants therefore request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

Matthew Beaudet
50,649; signing for

Date: April 7, 2003

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Tel: 617-239-0100

Marked-up Version of Amendment

Please **replace** claim 17, 23, 28, and 29 with the following claims.

17. (Amended) The method of claim 1 [, 15, or 16] wherein said ligand for CD40 of said CD40 ligand-enhanced cell comprises an exogenous engineered ligand for CD40.

23. (Amended) The method of claim 1 [, 15 or 16] wherein said CD40 ligand-enhanced cell is a pathogenic cell.

28. (Amended) The method of claim 1 [,15, 16, or 27] wherein said CD40 ligand-enhanced cell is substantially unable to divide in vitro.

29. (Amended) The method of claims 1 [, 15, 16, or 27] wherein said vaccine composition is attenuated.

70. (Amended) The method of claim [69] <u>23</u>, wherein said vaccine composition further comprises an opsonin-enhanced pathogenic cell, wherein said opsonin of said opsonin pathogenic cell is selected from the group consisting of mannose binding protein and the alpha' chain of c3b.

Exhibit A

☐ 1: P29965. Tumor necrosis fa...[gi:231718] BLink, Domains, Links

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LOCUS       TNF5_HUMAN               261 aa            linear   PRI 15-JUN-2002
DEFINITION  Tumor necrosis factor ligand superfamily member 5 (CD40 ligand)
            (CD40-L) (TNF-related activation protein) (TRAP) (T cell antigen
            Gp39) (CD154 antigen).
ACCESSION   P29965
VERSION     P29965  GI:231718
DBSOURCE    swissprot: locus TNF5_HUMAN, accession P29965;
            class: standard.
            created: Apr 1, 1993.
            sequence updated: Apr 1, 1993.
            annotation updated: Jun 15, 2002.
            xrefs: gi: 37269, gi: 37270, gi: 38483, gi: 38484, gi: 38411, gi:
            38412, gi: 180123, gi: 180124, gi: 662388, gi: 1518170, gi: 662386,
            gi: 664885, gi: 664886, gi: 662387, gi: 106153, gi: 284122, gi:
            284424, gi: 345789, gi: 345878, gi: 2554677
            xrefs (non-sequence databases): MIM 300386, MIM 308230,
            InterProIPR003263, InterProIPR003636, InterProIPR000478,
            PfamPF00229, ProDomPD008600, ProDomPD002012, SMARTSM00207,
            PROSITEPS00251, PROSITEPS50049
KEYWORDS    Cytokine; Transmembrane; Glycoprotein; Signal-anchor; Antigen;
            Disease mutation; Polymorphism; 3D-structure.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 261)
  AUTHORS   Graf,D., Korthauer,U., Mages,H.W., Senger,G. and Kroczek,R.A.
  TITLE     Cloning of TRAP, a ligand for CD40 on human T cells
  JOURNAL   Eur. J. Immunol. 22 (12), 3191-3194 (1992)
  MEDLINE   93076854
   PUBMED   1280226
  REMARK    SEQUENCE FROM N.A.
REFERENCE   2  (residues 1 to 261)
  AUTHORS   Hollenbaugh,D., Grosmaire,L.S., Kullas,C.D., Chalupny,N.J.,
            Braesch-Andersen,S., Noelle,R.J., Stamenkovic,I., Ledbetter,J.A.
            and Aruffo,A.
  TITLE     The human T cell antigen gp39, a member of the TNF gene family, is
            a ligand for the CD40 receptor: expression of a soluble form of
            gp39 with B cell co-stimulatory activity
  JOURNAL   EMBO J. 11 (12), 4313-4321 (1992)
  MEDLINE   93049181
   PUBMED   1385114
  REMARK    SEQUENCE FROM N.A.
REFERENCE   3  (residues 1 to 261)
  AUTHORS   Aruffo,A., Farrington,M., Hollenbaugh,D., Li,X., Milatovich,A.,
            Nonoyama,S., Bajorath,J., Grosmaire,L.S., Stenkamp,R., Neubauer,M.,
            Roberts,R.L., Noelle,R.J., Ledbetter,J.A., Francke,U. and Ochs,H.D.
```

TITLE The CD40 ligand, gp39, is defective in activated T cells from patients with X-linked hyper-IgM syndrome
JOURNAL Cell 72 (2), 291-300 (1993)
MEDLINE 93145330
PUBMED 7678782
REMARK SEQUENCE FROM N.A., AND VARIANTS HIGM1 128-ARG-GLY-129 AND PRO-235.
REFERENCE 4 (residues 1 to 261)
AUTHORS Spriggs,M.K., Armitage,R.J., Strockbine,L., Clifford,K.N., Macduff,B.M., Sato,T.A., Maliszewski,C.R. and Fanslow,W.C.
TITLE Recombinant human CD40 ligand stimulates B cell proliferation and immunoglobulin E secretion
JOURNAL J. Exp. Med. 176 (6), 1543-1550 (1992)
MEDLINE 93094757
PUBMED 1281209
REMARK SEQUENCE FROM N.A.
REFERENCE 5 (residues 1 to 261)
AUTHORS Gauchat,J.F., Aubry,J.P., Mazzei,G., Life,P., Jomotte,T., Elson,G. and Bonnefoy,J.Y.
TITLE Human CD40-ligand: molecular cloning, cellular distribution and regulation of expression by factors controlling IgE production
JOURNAL FEBS Lett. 315 (3), 259-266 (1993)
MEDLINE 93138085
PUBMED 7678552
REMARK SEQUENCE FROM N.A.
REFERENCE 6 (residues 1 to 261)
AUTHORS Shimadzu,M., Terasaki,H., Ninomiya,R., Shimizu,S., Nunoi,H. and Matsuda,I.
TITLE Direct Submission
JOURNAL Submitted (??-FEB-1995)
REMARK SEQUENCE FROM N.A.
REFERENCE 7 (residues 1 to 261)
AUTHORS Pietravalle,F., Lecoanet-Henchoz,S., Blasey,H., Aubry,J.P., Elson,G., Edgerton,M.D., Bonnefoy,J.Y. and Gauchat,J.F.
TITLE Human native soluble CD40L is a biologically active trimer, processed inside microsomes
JOURNAL J. Biol. Chem. 271 (11), 5965-5967 (1996)
MEDLINE 96198042
PUBMED 8626375
REMARK SEQUENCE OF 113-117, AND PROCESSING.
REFERENCE 8 (residues 1 to 261)
AUTHORS Karpusas,M., Hsu,Y.M., Wang,J.H., Thompson,J., Lederman,S., Chess,L. and Thomas,D.
TITLE 2 A crystal structure of an extracellular fragment of human CD40 ligand
JOURNAL Structure 3 (10), 1031-1039 (1995)
MEDLINE 96131874
PUBMED 8589998
REMARK X-RAY CRYSTALLOGRAPHY (2.0 ANGSTROMS) OF 116-261.
REFERENCE 9 (residues 1 to 261)
AUTHORS Singh,J., Garber,E., Van Vlijmen,H., Karpusas,M., Hsu,Y.M., Zheng,Z., Naismith,J.H. and Thomas,D.
TITLE The role of polar interactions in the molecular recognition of CD40L with its receptor CD40
JOURNAL Protein Sci. 7 (5), 1124-1135 (1998)
MEDLINE 98266353
PUBMED 9605317
REMARK 3D-STRUCTURE MODELING OF COMPLEX WITH CD40.
REFERENCE 10 (residues 1 to 261)
AUTHORS Korthauer,U., Graf,D., Mages,H.W., Briere,F., Padayachee,M., Malcolm,S., Ugazio,A.G., Notarangelo,L.D., Levinsky,R.J. and

Kroczek,R.A.
TITLE Defective expression of T-cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM
JOURNAL Nature 361 (6412), 539-541 (1993)
MEDLINE 93156839
PUBMED 7679206
REMARK VARIANTS HIGM1 ARG-36 AND GLY-140.
REFERENCE 11 (residues 1 to 261)
AUTHORS DiSanto,J.P., Bonnefoy,J.Y., Gauchat,J.F., Fischer,A. and de Saint Basile,G.
TITLE CD40 ligand mutations in x-linked immunodeficiency with hyper-IgM
JOURNAL Nature 361 (6412), 541-543 (1993)
MEDLINE 93156840
PUBMED 8094231
REMARK VARIANT HIGM1 GLU-123.
REFERENCE 12 (residues 1 to 261)
AUTHORS Allen,R.C., Armitage,R.J., Conley,M.E., Rosenblatt,H., Jenkins,N.A., Copeland,N.G., Bedell,M.A., Edelhoff,S., Disteche,C.M., Simoneaux,D.K., Fanslow,W.C., Belmont,J.W. and Spriggs,M.K.
TITLE CD40 ligand gene defects responsible for X-linked hyper-IgM syndrome
JOURNAL Science 259 (5097), 990-993 (1993)
MEDLINE 93174270
PUBMED 7679801
REMARK VARIANTS HIGM1 PRO-155; ASP-211 AND VAL-227.
REFERENCE 13 (residues 1 to 261)
AUTHORS Macchi,P., Villa,A., Strina,D., Sacco,M.G., Morali,F., Brugnoni,D., Giliani,S., Mantuano,E., Fasth,A., Andersson,B., Zegers,B.J.M., Cavagni,G., Reznick,I., Levy,J., Zan-Bar,I., Porat,Y., Airo,P., Plebani,A., Vezzoni,P. and Notarangelo,L.D.
TITLE Characterization of nine novel mutations in the CD40 ligand gene in patients with X-linked hyper IgM syndrome of various ancestry
JOURNAL Am. J. Hum. Genet. 56 (4), 898-906 (1995)
MEDLINE 95233438
PUBMED 7717401
REMARK VARIANTS HIGM1 ALA-126; ARG-140 AND GLU-144.
REFERENCE 14 (residues 1 to 261)
AUTHORS Lin,Q., Rohrer,J., Allen,R.C., Larche,M., Greene,J.M., Shigeoka,A.O., Gatti,R.A., Derauf,D.C., Belmont,J.W. and Conley,M.E.
TITLE A single strand conformation polymorphism study of CD40 ligand. Efficient mutation analysis and carrier detection for X-linked hyper IgM syndrome
JOURNAL J. Clin. Invest. 97 (1), 196-201 (1996)
MEDLINE 96133533
PUBMED 8550833
REMARK VARIANTS HIGM1 PRO-155 AND VAL-227, AND VARIANT ARG-219.
REFERENCE 15 (residues 1 to 261)
AUTHORS Nonoyama,S., Shimadzu,M., Toru,H., Seyama,K., Nunoi,H., Neubauer,M., Yata,J. and Och,H.D.
TITLE Mutations of the CD40 ligand gene in 13 Japanese patients with X-linked hyper-IgM syndrome
JOURNAL Hum. Genet. 99 (5), 624-627 (1997)
MEDLINE 97295077
PUBMED 9150729
REMARK VARIANTS HIGM1 ARG-36; CYS-140; SER-231; MET-254 AND GLY-227 DEL.
COMMENT ----------

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            the EMBL outstation - the European Bioinformatics Institute.
            The original entry is available from http://www.expasy.ch/sprot
            and http://www.ebi.ac.uk/sprot
            ----------------------------------------------------------------.
            [FUNCTION] MEDIATES B-CELL PROLIFERATION IN THE ABSENCE OF
            CO-STIMULUS AS WELL AS IGE PRODUCTION IN THE PRESENCE OF IL-4.
            INVOLVED IN IMMUNOGLOBULIN CLASS SWITCHING.
            [SUBUNIT] Homotrimer.
            [SUBCELLULAR LOCATION] TYPE II MEMBRANE PROTEIN. ALSO EXISTS AS AN
            EXTRACELLULAR SOLUBLE FORM.
            [TISSUE SPECIFICITY] SPECIFICALLY EXPRESSED ON ACTIVATED CD4+
            T-LYMPHOCYTES.
            [PTM] The soluble form derives from the membrane form by
            proteolytic processing.
            [DISEASE] DEFECTS IN TNFSF5 ARE THE CAUSE OF AN X-LINKED
            IMMUNODEFICIENCY WITH HYPER-IGM (HIGM1), AN IMMUNOGLOBULIN ISOTYPE
            SWITCH DEFECT CHARACTERIZED BY ELEVATED CONCENTRATIONS OF SERUM IGM
            AND DECREASED AMOUNTS OF ALL OTHER ISOTYPES. AFFECTED MALES PRESENT
            AT AN EARLY AGE (USUALLY WITHIN THE FIRST YEAR OF LIFE) RECURRENT
            BACTERIAL AND OPPORTUNISTIC INFECTIONS, INCLUDING PNEUMOCYSTIS
            CARINII PNEUMONIA AND INTRACTABLE DIARRHEA DUE TO CRYPTOSPORIDIUM
            INFECTION. DESPITE SUBSTITUTION TREATMENT WITH INTRAVENOUS
            IMMUNOGLOBULIN, THE OVERALL PROGNOSIS IS RATHER POOR, WITH A DEATH
            RATE OF ABOUT 10% BEFORE ADOLESCENCE.
            [SIMILARITY] BELONGS TO THE TUMOR NECROSIS FACTOR FAMILY.
            [DATABASE] NAME=CD40Lbase; NOTE=European CD40L defect database
            (mutation db); WWW='http://www.expasy.org/cd40lbase/';
            FTP='ftp://ftp.expasy.org/databases/cd40lbase'.
            [DATABASE] NAME=PROW; NOTE=CD guide CD154 entry;
            WWW='http://www.ncbi.nlm.nih.gov/prow/cd/cd154.htm'.
FEATURES            Location/Qualifiers
     source         1..261
                    /organism="Homo sapiens"
                    /db_xref="taxon:9606"
     gene           1..261
                    /gene="TNFSF5"
                    /note="synonyms: CD40LG, CD40L, TRAP"
     Protein        1..261
                    /gene="TNFSF5"
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                    5"
     Region         1..261
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                    /note="TUMOR NECROSIS FACTOR LIGAND SUPERFAMILY MEMBER 5,
                    MEMBRANE FORM."
     Region         1..22
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                    /region_name="Domain"
                    /note="CYTOPLASMIC (POTENTIAL)."
     Region         23..46
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                    /note="SIGNAL-ANCHOR (TYPE-II MEMBRANE PROTEIN)
                    (POTENTIAL)."
     Region         36
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     Region         47..261
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                     /note="EXTRACELLULAR (POTENTIAL)."
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                     /note="CLEAVAGE."
     Region          113..261
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                     /note="TUMOR NECROSIS FACTOR LIGAND SUPERFAMILY MEMBER 5,
                     SOLUBLE FORM."
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     Region          123
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                     /region_name="Variant"
                     /note="A -> E (IN H1GM1). /FTId=VAR_007514."
     Region          126
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                     /region_name="Variant"
                     /note="V -> A (IN H1GM1). /FTId=VAR_007515."
     Region          128..129
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                     /region_name="Variant"
                     /note="SE -> RG (IN H1GM1). /FTId=VAR_007516."
     Region          137
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     Region          140..141
                     /gene="TNFSF5"
                     /region_name="Beta-strand region"
     Region          140
                     /gene="TNFSF5"
                     /region_name="Variant"
                     /note="W -> C (IN H1GM1). /FTId=VAR_007517."
     Region          140
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                     /note="W -> G (IN H1GM1). /FTId=VAR_007518."
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                     /note="W -> R (IN H1GM1). /FTId=VAR_007519."
     Region          144
                     /gene="TNFSF5"
                     /region_name="Variant"
                     /note="G -> E (IN H1GM1). /FTId=VAR_007520."
     Region          147..148
                     /gene="TNFSF5"
                     /region_name="Beta-strand region"
     Region          151..152
                     /gene="TNFSF5"
                     /region_name="Hydrogen bonded turn"
     Region          153..156
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                     /region_name="Beta-strand region"
     Region          155
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     Region          160..163
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                     /region_name="Beta-strand region"
     Region          167..179
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                     /gene="TNFSF5"
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     Region          188..195
                     /gene="TNFSF5"
                     /region_name="Beta-strand region"
     Region          198..199
                     /gene="TNFSF5"
                     /region_name="Hydrogen bonded turn"
     Region          203..211
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                     /region_name="Beta-strand region"
     Region          211
                     /gene="TNFSF5"
                     /region_name="Variant"
                     /note="T -> D (IN H1GM1). /FTId=VAR_007522."
     Region          214..215
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                     /region_name="Hydrogen bonded turn"
     Region          219..232
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     Region          219
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                     /note="G -> R. /FTId=VAR_007523."
     Region          227
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                     /region_name="Variant"
                     /note="G -> V (IN H1GM1). /FTId=VAR_007524."
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                     /region_name="Variant"
                     /note="MISSING (IN H1GM1). /FTId=VAR_007525."
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                     /region_name="Variant"
                     /note="L -> S (IN H1GM1). /FTId=VAR_007526."
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                     /region_name="Hydrogen bonded turn"
     Region          235
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     Region          235
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                     /region_name="Beta-strand region"
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                     /site_type="glycosylation"
                     /note="N-LINKED (GLCNAC...) (POTENTIAL)."
     Region          244..246
                     /gene="TNFSF5"
                     /region_name="Helical region"
     Region          247
                     /gene="TNFSF5"
                     /region_name="Beta-strand region"
     Region          254
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                     /region_name="Variant"
                     /note="T -> M (IN H1GM1). /FTId=VAR_007528."
     Region          255..261
                     /gene="TNFSF5"
                     /region_name="Beta-strand region"
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       61 edfvfmktiq rcntgersls llnceeiksq fegfvkdiml nkeetkkens femqkgdqnp
      121 qiaahvisea sskttsvlqw aekgyytmsn nlvtlengkq ltvkrqglyy iyaqvtfcsn
      181 reassqapfi aslclkspgr ferillraan thssakpcgq qsihlggvfe lqpgasvfvn
      241 vtdpsqvshg tgftsfgllk l
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Revised: August 5, 2002.

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